HFA-305

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FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

ANADA 200-253

ProstaMate™ (dinoprost tromethamine injection) Sterile Solution

For intramuscular use for estrus synchronization, treatment of unobserved (silent) estrus and pyometra (chronic endometritis) in cattle: for abortion of feedlot and other non-lactating cattle; for parturition induction in swine; and for controlling the timing of estrus in estrous cycling mares and clinically anestrous mares that have a corpus luteum.

Sponsored by:

Phoenix Scientific, Inc.
3915 South 48th Street Terrace
P.O. Box 6457
St. Joseph, MO 64506-0457

ANADA 200-253

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FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

ANADA Number:	200-253
Sponsor:	Phoenix Scientific, Inc. 3915 South 48th Street Terrace P.O. Box 6457 St. Joseph, MO 64506-0457
Generic Name:	dinoprost tromethamine, USP
Trade Name:	ProstaMate™ (dinoprost tromethamine injection) Sterile Solution
Dosage Form:	injectable solution
How Supplied:	10 mL and 30 mL multiple dose vials
How Dispensed:	Rx
Amount of Active Ingredients:	Each mL contains 5 mg of dinoprost from dinoprost tromethamine
Route of Administration:	IM Injection
Species:	Cattle, swine, horses
Labeled Dosage	Cattle -5 mL IM Swine -2 mL IM Mares -1 mL IM
Indications for Use:	For intramuscular use for estrus synchronization, treatment of unobserved (silent) estrus and pyometra (chronic endometritis) in cattle: for abortion of feedlot and other non-lactating cattle; for parturition induction in swine; and for controlling the timing of estrus in estrous cycling mares and clinically anestrous mares that have a corpus luteum.

2. TARGET ANIMAL SAFETY AND DRUG EFFECTIVENESS

Under the provisions of the Federal Food, Drug and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (53 FR 50460, December 15, 1988, First GADPTRA Policy Letter) an abbreviated new animal drug application (ANADA) maybe submitted for a generic version of an approved new animal drug (pioneer product).

For certain dosage forms, the agency grants a waiver from conducting an *in vivo* bioequivalence study (55 FR 24645, June 18, 1990: fifth GADPTRA Policy Letter). In lieu of bioequivalence testing, the safety and efficacy of the generic product are-based on the demonstrated chemical equivalence to the pioneer product.

Based upon the formulation characteristics of the generic product, Phoenix Scientific, Inc. was granted a waiver from conducting an *in vivo* bioequivalence study with ProstaMate™ (dinoprost tromethamine injection). The generic and pioneer products are solutions with the same active and inactive ingredients.

3. HUMAN SAFETY

Human Food Safety

Cattle: No Milk discard or preslaughter drug withdrawal period is required for labeled uses.
Swine: No preslaughterdrug withdrawal period is required for labeled uses.
Mares: Not for use in horses intended for food.

Human Safety Relative to Possession, Handling and Administration:

The labeling contains adequate Warning statements, as described below.

Not for human use.

Women of childbearing age, asthmatics, and persons with bronchial and other respiratory problems should exercise extreme caution when handling this product. In the early stages, women maybe unaware of their pregnancies. Dinoprost tromethamine is readily absorbed through the skin and can cause abortion and/or bronchospasms. Direct contact with the skin should, therefore, be avoided. Accidental spillage on the skin should be washed off immediately with soap and water.

4. AGENCY CONCLUSION:

This ANADA submitted under section 5 12(b) of the Federal Food, Drug and Cosmetic Act satisfies the requirements of section 512(n) of the Act and demonstrates that ProstaMate™ (dinoprost tromethamine injection) Sterile Solution, when used under the proposed conditions of use, is safe and effective for the labeled indications.

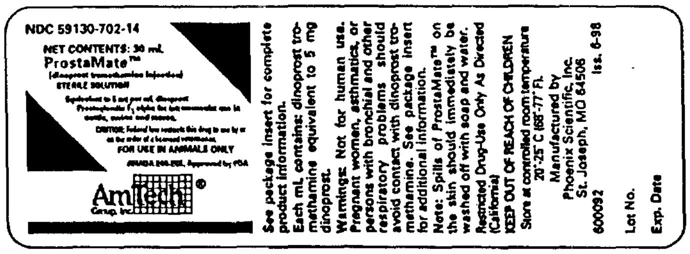
Attachments:

1. Generic Labeling:

   Vial Label
   Package Insert
   Carton Label

2. Pioneer Labeling

   Vial Label
   Package Insert
   Carton Label



NDC 59130-702-14

NET CONTENTS: 30 mL

ProstaMate™

(dinoprost trometfrsrmirre injection)

STERILE SOLUTION

Equivalent to 5 mg per ml dinoprost Prostaglandin F_2 alpha for intramuscular use in cattle, swine and mares.

CAUTION: Federal law restricts this drug 10 use by or on the order of a licensed veterinarian

FOR USE IN ANIMALS ONLY

WA 200-2S3. Approved by FDA

AmTech® Group, Inc.

See package insert for complete product information.

Each mL contains: dinoprost tromethamine equivalent to 5 mg dinoprost.

Warnings: Not for human use. Pregnant women, asthmatics, or persons with bronchial and other respiratory problems should avoid contact with dinoprost tromethamine. See package insert for additional information.

Note: Spills of ProstaMate™ on the skin should immediately be washed off with soap and water.

Restricted Drug-Use Only As Directed (California)

KEEP OUT OF REACH OF CHILDREN

Store at controlled room temperature 20"-25" C (68"-77" F).

Manufactured by
Phoenix Scientific, Inc.
St. Joseph, MO 64506

600092 Iss. 6-98

Lot No.

Exp. Date

CUSTOMER PROOF • CHECK CAREFULLY!

Customer: Phoenix Scientific P.O. # Proof

CYREL #: 23325 (sh) 'ate Sent: 8/19/97 9/9/97 6/11/98 6[24/98

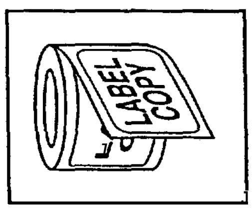
LABEL: AmTech's Prostamate 30 mL

UNWIND #:4

SIZE: 1.25 x 3.5 inches

PATTERN VARNISH: ‘ater

COLORS: 1797 ‘ed black



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Every effort has been taken to insure the accuracy and conformance to applicable regulations on this proof. However, please check carefully as the final liability rests with the customer.

Approved by: ______________ Date approved: ______________

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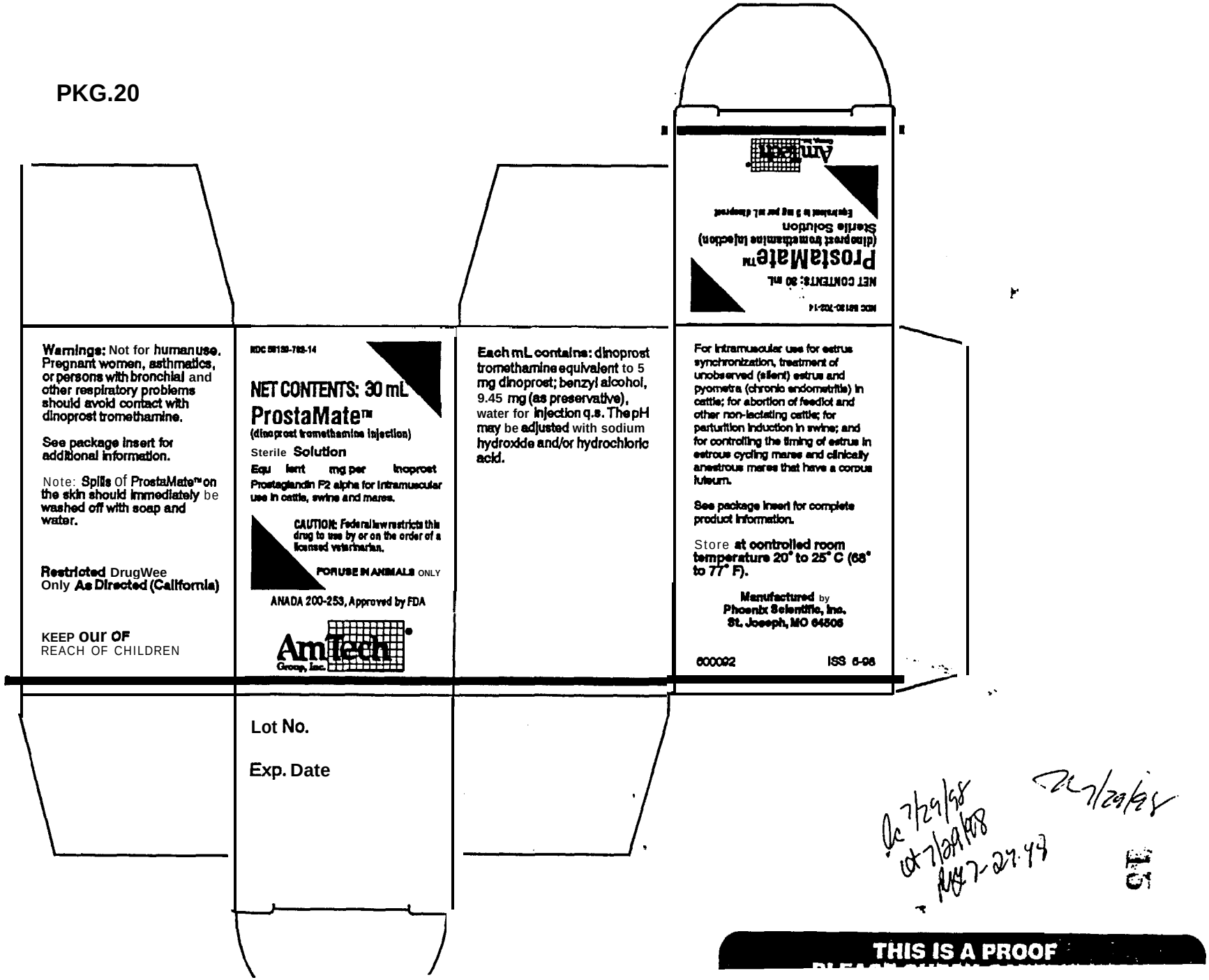

7/29/98
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7-27-98

THIS IS A PROOF

ANADA 200-253, Approved by FDA

ProstaMate™

(dinoprost tromethamine injection)
Sterile Solution

Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

For intramuscular use for estrus synchronization, treatment of unobserved (silent) estrus and pyometra (chronic endometritis) in cattle; for abortion of feedlot and other non-lactating cattle; for parturition induction in swine; and for controlling the timing of estrus in estrous cycling mares and clinically anestrous mares that have a corpus ...

DESCRIPTION

...roduct contains the naturally occurring prostaglandin F2 alpha (dinoprost) as the tromethamine salt. Each mL ...ns dinoprost tromethamine equivalent to 5 mg dinoprost: also, benzyl alcohol, 9.45 mg added as preservative. When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid. Dinoprost tromethamine is a white or slightly off-white crystalline powder that is readily soluble in water at room temperature in concentrations to at least 200 mg/mL.

General Biologic Activity: Prostaglandins occur in nearly all mammalian tissues. Prostaglandins, especially PGE's and PGF's, have been shown, in certain species, to 1) increase at time of parturition in amniotic fluid, maternal placenta, myometrium, and blood, 2) stimulate myometrial activity, and 3) to induce either abortion or parturition. Prostaglandins, especially PGF2α, have been shown to 1) increase in the uterus and blood to levels similar to levels achieved by exogenous administration which elicited luteolysis, 2) be capable of crossing from the uterine vein to the ovarian artery (sheep), 3) be related to IUD induced luteal regression (sheep), and 4) be capable of regressing the corpus luteum of most mammalian species studied to date. Prostaglandins have been reported to result in release of pituitary tropic hormones. Data suggest prostaglandins, especially PGE's and PGF's, may be involved in the process of ovulation and gamete transport. Also PGF2α have been reported to cause increase in blood pressure, bronchoconstriction, and smooth muscle stimulation in certain species.

Laboratory Animals: Dinoprost was non-teratogenic in rats when administered orally at 1.25, 3.2, 10.0 and 20.0 mg/kg/day from day 6th-15th of gestation or when administered subcutaneously at 0.5 and 1.0 mg/kg/day on gestation days 6, 7 and 8 or 9, 10 and 11 or 12, 13 and 14. Dinoprost was non-teratogenic in the rabbit when administered either subcutaneously at doses of 0.5 and 1.0 mg/kg/day on gestation days 6, 7 and 8 or 9, 10 and 11 or 12, 13 and 14 or 15, 16 and 17 or orally at doses of 0.01, 0.1 and 1.0 mg/kg/day on days 6-18 or 5.0 mg/kg/day on days 6-18 of gestation. A slight and marked embryo lethal effect was observed in dams given 1.0 and 5.0 mg/kg/day respectively. This was due to the expected luteolytic properties of the drug.

A 14-day continuous intravenous infusion study in rats at 20 mg PGF2α per kg body weight indicated prostaglandins of the F series could induce bone deposition. However, such bone changes were not observed in monkeys similarly administered dinoprost tromethamine sterile solution at 15 mg PGF2α per kg body weight for 14 days.

Cattle: In cattle, evaluation was made of clinical observations, clinical chemistry, hematology, urinalysis, organ weights, and gross plus microscopic measurements following treatment with various doses up to 250 mg dinoprost administered twice intramuscularly at a 10 day interval or doses of 25 mg administered daily for 10 days. There was no unequivocal effect of dinoprost on the hematology or clinical chemistry parameters measured. Clinically, a slight transitory increase in heart rate was detected. Rectal temperature was elevated about 1.5° F through the 6th hour after injection with 250 mg dinoprost, but had returned to baseline at 24 hours after injection. No dinoprost associated gross lesions were detected. There was no evidence of toxicological effects. Thus, dinoprost had a safety factor of at least 10X on injection (25 mg luteolytic dose vs. 250 mg safe dose), based on studies conducted with cattle. At luteolytic doses, dinoprost had no effect on progeny. If given to a pregnant cow, it may cause abortion; the dose required for abortion varies considerably with the stage of gestation.

Induction of abortion in feedlot cattle at stages of gestation up to 100 days of gestation did not result in dystocia, retained placenta or death of heifers in the field studies. The smallness of the fetus at this early stage of gestation should not lead to complications at abortion. However, induction of parturition or abortion with any exogenous compound may precipitate dystocia, fetal death, retained placenta and/or metritis, especially at latter stages of gestation.

Swine: In pigs, evaluation was made of clinical observations, food consumption, clinical pathologic determinations, body weight changes, urinalysis, organ weights, and gross and microscopic observations following treatment with single doses of 10, 30, 50 and 100 mg dinoprost administered intramuscularly. The results indicated no treatment related effects from dinoprost treatment that were deleterious to the health of the animals or to their offspring.

Mares: Dinoprost tromethamine was administered to adult mares (weighing 320 to 485 kg; 2 to 20 years old), at the rates of 0, 100, 200, 400, and 800 mg per mare per day for 8 days. Route of administration for each dose group was both intramuscularly (2 mares) and subcutaneously (2 mares). Changes were detected in all treated groups for clinical (reduced sensitivity to pain; locomotor incoordination; hypergastromotility; sweating; hyperthermia; labored respiration), blood chemistry (elevated cholesterol, total bilirubin, LDH, and glucose), and hematology (decreased eosinophils; increased hemoglobin, hematocrit, and erythrocytes) measurements. The effects in the 100 mg dose, and to a lesser extent, the 200 mg dose groups were transient in nature, lasting ... a few minutes to several hours. Mares did not appear to sustain adverse effects following termination of the side ...

Mares treated with either 400 mg or s00 mg ... gastrointestinal tract caused a protracted diarrhea slight elec “ ” ’ - ’ R G ? = : 2 2 : % ; F A : F : G . : G dehydration, gastrointestinal irritation, and slight ... function (elev .led SGOT, SOPT at 800 mg only Hint! rate was increased but pH of the urine was decreas Other measurements ● valuated h the study remained w h normal limits. No mortality occurred h any d the groups. No apparent differences were observed between the intramuscular and ...neous routes d administration. Luteolytic doses d dinoprost tromethamine are on the order d 5 20 10 mg ...ered on one day, therefore, dinoprost tromethamine sterile solution was demonstrated b have a wide margin of ... Thus, the 100 mg dose gave a safety margin of 10 to 20X for a single injection or 80 to 160X for the 8 daily ...ons.

Additional studies investigated the effects h the mare d single intramuscular doses d o, 0.2s. 1.0,25.3.0,5.0. and 10.0 mg dinoprost tromethamine. Heart rate, respiration rate, rectal temperature, and sweating were measured at 0, 0.22.0.50, 0.75, 1.0, 1.5, 2.0, so. 4.0.5.0, and 6.0 hr. after injection. Neither heart rate nor respiration rates were significantly altered (P > 0.05) when compared to contemporary control values. Sweating was observed fo0 of 9, 2 of 9, 7 of 9, 9 of 9, and 8 of 9 mares injected with 0.25, 1.0, 2.5, 30.S00. or 10.0 mg dinoprost tromethamine, respectively. Sweating was temporary in all cases and was mild for doses of 3.0 mg or less but was extensive (beads of sweat over the entire body and dripping) for the 10 mg dose. Sweating after the 5.0 mg dose was intermediate between that seen for mares treated with 3.0 and 10.0 mg. Sweating began within 15 minutes after injection and ceased by 4S to 20 minutes after injection. Rectal temperature was decreased during the interval 0.5 until 1.0. 3 to 4. or 5 hours after injection for 0.25 and 1.0 mg. 2.5 and 3.0, or 5.0 and 10.0 mg dose groups, respectively. Average rectal temperature during the periods d decreased temperature was on the order of 97.5 to 99.6, with the greatest decreases observed h the 10 mg dose group.

METABOLISM

A number of metabolism studies have been done in laboratory animals. The metabolism of tritium labeled dinoprost (^{3}H PGF2 alpha) in the rat and in the monkey was similar. Although quantitative differences were observed, qualitatively similar metabolites were produced. A study demonstrated that equimolar doses of ^{3}H PGF2 alpha Tham and ^{3}H PGF2 alpha free acid administered intravenously to rats demonstrated no significant differences in blood concentration of dinoprost. An interesting observation in the above study was that the radioactive dose of ^{3}H PGF2 alpha rapidly distributed in tissues and dissipated in tissues with almost the same curve as it did in the serum. The half-life of dinoprost in bovine blood has been reported to be on the order of minutes. A complete study on the distribution of decline of ^{3}H PGF2 alpha Tham in the tissue of rats was well correlated with the work done in the cow. Cattle serum collected during 24 hours after doses of 0 to 250 mg dinoprost have been assayed by RIA for dinoprost and the 15-keto metabolites. These data support previous reports that dinoprost has a half-life of minutes. Dinoprost is a natural prostaglandin. All systems associated with dinoprost metabolism exist in the body; therefore, no new metabolic, transport, excretory, binding or other systems need be established by the body to metabolize injected dinoprost.

INDICATIONS AND INSTRUCTIONS FOR Uss

Cattle: ProstaMate™ Sterile Solution k indicated as a luteolytic agent.

ProstaMate™ b effective only h those cattle having a corpus luteum, i.e., those which ovulated at least five days prior to treatment. Future reproductive performance of animals that are not cycling will be unaffected by injection d ProstaMate™.

1. **For Intramuscular Use for Estrus Synchronization in Beef Cattle and Non-Lactating Dairy Heifers.** ProstaMate™ is used to control the timing of estrus and ovulation in estrous cycling cattle that have a corpus luteum.
   Inject a dose of 5 mL ProstaMate™ (25 mg PGF2α) intramuscularly either once or twice at a 10 to 12 day interval.
   With the single injection, cattle should be bred at the usual time relative to estrus. With the two injections cattle can be bred after the second injection either at the usual time relative to detected estrus or at about 80 hours after the second injection of ProstaMate™.
   Estrus is expected to occur 1 to 5 days after injection if a corpus luteum was present. Cattle that do not become pregnant to breeding at estrus on days 1 to 5 after injection will be expected to return to estrus in about 18 to 24 days.
2. **For Intramuscular Use for Unobserved (Silent) Estrus In Lactating Dairy Cows with a Corpus Luteum.** Inject . dose d 5 mL ProstaMate™ (25 mg PGF2α) intramuscularly. Breed cows as they are detected h estrus. H estrus has not been observed by so hours after injection, eed ● so hours. If the cow returns to ● SINS breed at the usual time relative to estrus.

Management Considerations: Many factors contribute to success and failure d reproduction management, and these factors are important also when time d breeding k to be regulated with ProstaMate™ Sterile Solution. Some d these factors are:

a. Cattle must be ready to breed- they must have a corpus luteum and be healthy;
b. Nutritional status must be adequate as this has a direct effect on conception and the initiation of estrus in heifers or return of estrous cycles in cows following calving;
c. Physical facilities must be adequate to allow cattle handling without being detrimental to the animal;
d. Estrus must be detected accurately if timed AI is not employed;
e. Semen of high fertility must be used;
f. Semen must be inseminated properly.

A successful breeding program can employ ProstaMate™ effectively, but a poorly managed breeding program will continue to be poor when ProstaMate™ is employed unless other management deficiencies are remedied first.

... expressing estrus following ProstaMate™ are receptive to breeding by a bull. Using bulls to breed large numbers of ... heat following ProstaMate™ will require proper management of bulls and cattle.

... **Intramuscular Use for Treatment of Pyometra (chronic endometritis) in Cattle.** Inject a dose of 5 mL ...Mate™ (25 mg PGF2α) intramuscularly. In studies conducted with dinoprost tromethamine sterile solution, pyometra was defined as presence of a corpus luteum in the ovary and uterine horns containing fluid but not a conceptus based on palpation *per rectum*. Return to normal was defined as evacuation of fluid and return of the uterine horn size to 40 mm or less based on palpation *per rectum* at 14 and 28 days. Most cattle that recovered in response to ProstaMate™ recovered within 14 days after injection. After 14 days, recovery rate of treated cattle was no different than that of non-treated cattle.

4. **For Intramuscular Use for Abortion of Feedlot and Other Non-Lactating Cattle.** ProstaMate™ is indicated for its abortifacient effect in feedlot and other non-lactating cattle during the first 100 days of gestation. Inject a dose of 25 mg intramuscularly. Cattle that abort will abort within 35 days of injection.

Commercial cattle were palpated *per rectum* for pregnancy in six feedlots. The percent of pregnant cattle in each feedlot less than 100 days of gestation ranged between 26 and 94; 80% or more of the pregnant cattle were less than 150 days of gestation. The abortion rates following injection of dinoprost tromethamine sterile solution increased with increasing doses up to about 25 mg. As examples, the abortion rates, over 7 feedlots on the dose titration study, were 22%, 50%, 71%, 90% and 78% for cattle up to 100 days of gestation when injected IM with dinoprost tromethamine sterile solution doses of 0.1 (5 mg), 2 (10 mg), 4 (20 mg) and 8 (40 mg) mL, respectively. The statistical predicted relative abortion rate based on the dose titration data, was about 93% for the 5 mL (25 mg) ...

...ine: For intramuscular use for parturition induction in swine. ProstaMate™ Sterile Solution is indicated for parturition ...ction in swine when injected within 3 days of normal predicted farrowing.

...e response to treatment varies by individual animals with a mean interval from administration of 2 mL ProstaMate™ (10 mg dinoprost) to parturition of approximately 30 hours. This can be employed to control the time of farrowing in sows and gilts in late gestation.

...nagement Considerations: Several factors must be considered for the successful use of ProstaMate™ Sterile Solution ... parturition induction in swine. The product must be administered at a relatively specific time (treatment earlier than 3 ...s prior to normal predicted farrowing may result in increased piglet mortality). It is important that adequate records be ...intained on (1) the average length of gestation period for the animals on a specific location, and (2) the breeding and ...jected farrowing dates for each animal. This information is essential to determine the appropriate time for administration ...ProstaMate™.

...res: ProstaMate™ Sterile Solution is indicated for its luteolytic effect in mares. This luteolytic effect can be utilized to ...trol the timing of estrus in estrous cycling and clinically anestrous mares that have a corpus luteum in the following ...cumstances:

Controlling Time of Estrus of Estrous Cycling Mares: Mares treated with ProstaMate™ during diestrus (4 or more ...days after ovulation) will return to estrus within 2 to 4 days in most cases and ovulate 8 to 12 days after treatment. This ...procedure may be utilized as an aid to scheduling the use of stallions.

Difficult-to-Breed Mares: In extended diestrus there is failure to exhibit regular estrous cycles which is different from ...rue anestrus. Many mares described as anestrus during the breeding season have serum progesterone levels ...consistent with the presence of a functional corpus luteum.

A proportion of "barren", maiden, and lactating mares do not exhibit regular estrous cycles and may be in extended ...diestrus. Following abortion, early fetal death and resorption, or as a result of "pseudopregnancy", there may be serum ...progesterone levels consistent with a functional corpus luteum.

Treatment of such mares with ProstaMate™ usually results in regression of the corpus luteum followed by estrus ...and/or ovulation. In one study with 122 Standardbred and Thoroughbred mares in clinical anestrus for an average of 58 ...days and treated during the breeding season, behavioral estrus was detected in 81 percent at an average time of 3.7 ...days after injection with 5 mg dinoprost tromethamine sterile solution; ovulation occurred an average of 7.0 days after ...treatment. Of those mares bred, 59% were pregnant following an average of 1.4 services during that estrus.

Treatment of "anestrous" mares which abort subsequent to 36 days of pregnancy may not result in return to estrus due ...to presence of functional endometrial cups.

WARNINGS

...ot for human use.

...Women of child-bearing age, asthmatics, and persons with bronchial and other respiratory problems should exercise ...treme caution when handling this product. In the early stages, women may be unaware of their pregnancies. Dinoprost ...methamine is readily absorbed through the skin and can cause abortion and/or bronchiospasms. Direct contact with the ...in should, therefore, be avoided. Accidental spillage on the skin should be washed off immediately with soap and water.

...se of this product h excess d the approved dose may result h drug residues.

PRECAUTIONS

...attle: 00 not administer to pregnant cattle unless abortion k desired.

b not administer intravenously (I.V.), as this route might potentiate adverse reactions.

...attle administered ● progestogen would be ● l@edd to have ● reduced response to ProstaMate™ Sterile Solution.

Aggressive antibiotic therapy should be employed at th the first sign of infection at the injection site whether localized or diffuse. As with all parenteral ... careful aseptic techniques should be employed to decrease the possibility of post ...jection bacterial infections.

...wine: Do not administer to sows and/or gilts prior to 3 days of normal predicted farrowing, as increased number of ...illborn and postnatal mortality may result.

...ares: ProstaMate™ Sterile Solution b ineffective when administered prior b day-5 after ovulation.

...Pregnancy status should be determined prior b treatment, since ProstaMate™ has been reported to induce abortion and ...arturition when sufficient doses were administered.

...Mares should not be treated if they suffer from either acute or ● &c@, disorders d the vascular system, gastrointestinal ...act, respiratory system, or reproductive tract.

...Do not administer by intravenous route.

...Nonsteroidal anti-inflammatory drugs (i.e., indomethacin) may inhibit prostaglandin synthesis, therefore these drugs ...would not be administered concurrently.

ADVERSE REACTIONS

...attle:

. The most frequently observed side effect is increased rectal temperature at a 5X or 10X overdose. However, rectal temperature change has been transient in all cases observed and has not been detrimental to the animal.
. Limited salivation has been reported in some instances.
. Intravenous administration might increase heart rate.
. Localized post injection bacterial infections that may become generalized have been reported. In rare instances such infections have terminated fatally. See PRECAUTIONS.

...wine: The most frequently observed side effects were erythema and pruritus, slight incoordination, nesting behavior, ...ching, urination, defecation, abdominal muscle spasms, tail movements, hyperpnea or dyspnea, increased vocalization, ...alivation, and at the 100 mg (10X) dose only, vomition. These side effects are transitory, lasting from 10 minutes to 3 ...ours, and were not detrimental to the health of the animal.

...Mares: The most frequently observed side effects are sweating and decreased rectal temperature. However, these have ...been transient in all cases observed and have not been detrimental to the animal. Other reactions seen have been ...increase in heart rate, increase in respiration rate, some abdominal discomfort, locomotor incoordination, and lying down. ...These effects are usually seen within 15 minutes of injection and disappear within one hour. Mares usually continue to eat ...during the period of expression of side effects. One anaphylactic reaction of several hundred mares treated with dinoprost ...tromethamine sterile solution was reported but was not confirmed.

IMPORTANT

Cattle: No milk discard or preslaughter drug withdrawal period is required for labeled uses

Swine: No preslaughter drug withdrawal period b required for labeled uses.

Mares: Not for use h horses intended for bad.

DOSAGE AND ADMINISTRATION

Cattle: ProstaMate™ Sterile Solution b supplied at a concentration d 5 mg dinoprost per ML. ProstaMate™ b luteolytic in cattle at 25 mg (5 mL administered intramuscularly. As with any multidose vial, practice aseptic techniques h withdrawing each dose. Adequately clean and disinfect the vial closure prior to entry with a sterile needle.

Swine: ProstaMate™ Sterile Solution will induce parturition h swine at 10 mg (2 mL) when injected intramuscularly.

AS with any multidose vial, practice ● mplk techniques h withdrawing each dose. Adequately clean and disinfect the vial closure prior to entry with ● sterile needle.

Mares:

1. Evaluate the reproductive status d the mare.
2. Administer ● single intramuscular injection d 1 mg per 100 lbs. (45.6 kg) body weight which b usually 1 mL to 2 mL ProstaMate m Sterile Solution.
3. Observe for signs of estrus by means of daily teasing with a stallion, and evaluate follicular changes on the ovary by palpation d the ovary *per rectum*.
4. Some clinically anestrous mares will not express estrus but will develop a follicle which will ovulate. These mares may become pregnant if inseminated d the appropriate time relative to rupture d the follicle.
S. Breed mares h ● lna h ● manner consistent with normal management.

Dinoprost tromethamine is administered once as a single intramuscular injection ... (45.6 kg) body weight which is usually 1 mL to 2 mL of ProstaMate™ containing 5 mg dinoprost as the tromethamine salt per milliliter.

HOW SUPPLIED

ProstaMate™ Sterile Solution b available h 10 and 30 mL vials.

STORAGE CONDITIONS

Store at controlled room l-alumN102s' c (68° to 77° F).

Manufactured by
Phoenix Scientific, Inc.
St. Joseph, MO 64506

600092

Iss. 6-98

NDC 0009-0327-03 10 mL

Lutalyse®

Sterile Solution

dinoprost tromethamine injection

Equivalent to

5 mg per mL

dinoprost

For Intramuscular use

Restricted Drug–Use Only as Directed (California)

For Use in Animals Only

See package insert for complete product information.

Warnings: Not for human use. Pregnant women, asthmatics, or persons with bronchial and other respiratory problems should avoid contact with dinoprost tromethamine. See package insert for additional information.

Note: Spills of LUTALYSE on the skin should immediately be washed off with soap and water.

Store at controlled room temperature 15°-30° C (59°-86° F).

Each mL contains: Dinoprost tromethamine equivalent to 5 mg dinoprost.

810 458 207

NDC 0009-0327-03
One 10 mL Vial
Lutalyse
Sterile Solution
dinoprost tromethamine injection
Equivalent to
5 mg per mL
dinoprost

For intramuscular use for estrus synchronization, treatment of unobserved (silent) estrus and pyometra (chronic endometritis) in cattle; for abortion of feedlot and other non-lactating cattle; for parturition induction in swine; and for controlling the timing of estrus in estrous cycling mares and clinically anestrous mares that have a corpus luteum.

See package insert for complete product information.

Warnings: Not for human use. Pregnant women, asthmatics, & persons with bronchial respiratory problems should avoid contact with dinoprost tromethamine. See package insert for additional information.

Note: Spills of LUTALYSE on the skin should immediately be washed off with soap and water

Store at controlled room temperature 15°-30°C (59°-86°F)

Each mL contains: Dinoprost tromethamine equivalent to 5 mg dinoprost; benzyl alcohol, 9.45 mg added as preservative.

When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid.

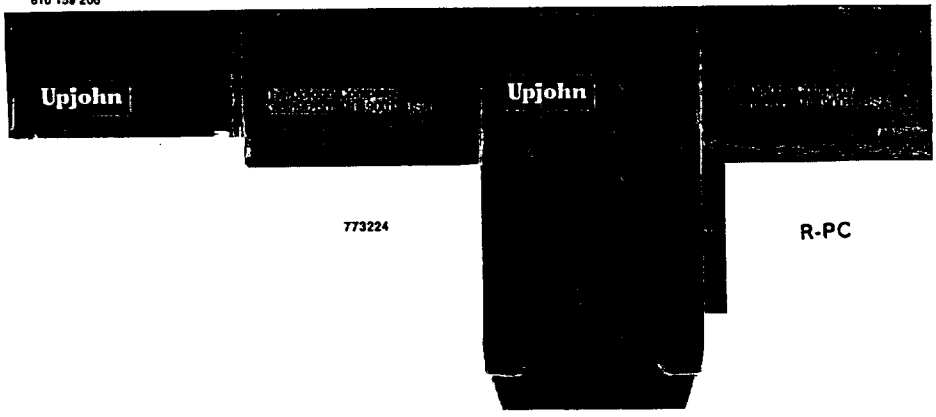
NDC 0009-0327-03
Ona 10 mL Vial
Lutalyse®
Sterile Solution
dinoprost tromethamine injection
Equivalent to
5 mg per mL
dinoprost

Prostaglandin F_2 alpha for intramuscular use in cattle, swine and mares.

Restricted Drug–Use Only as Directed (California)

For Use in Animals Only

Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.



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R-PC

000147

NDC 0009-0327-10 30 mL

Lutalyse®

Sterile Solution

dinoprost tromethamine injection

Equivalent to

5 mg per mL

dinoprost

For Intramuscular use

Restricted Drug—Use Only As Directed (California)

For Use In Animals Only

See package insert for complete product information.

Warnings: Not for human use. Pregnant women, asthmatics, or persons with bronchial and other respiratory problems should avoid contact with dinoprost tromethamine. See package insert for additional information.

Note: Spills of LUTALYSE on the skin should immediately be washed with soap and water.

Store at controlled room temperature 20° to 25° C (68° to 77° F) [see USP]

Each mL contains: dinoprost tromethamine equivalent to 5 mg dinoprost

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[redacted]

[redacted]

5 mg per mL dinoprost

Lutalyse

Sterile Solution

dinoprost tromethamine injection

Equivalent to

One 30 mL Vial

NDC 0009-0327-10

For intramuscular use for estrus synchronization, treatment of unobserved (silent) estrus and pyometra (chronic endometritis) in cattle; for abortion of feedlot and other non-lactating cattle; for parturition induction in swine; and for controlling the timing of estrus in estrous cycling mares and clinically anestrous mares that have a corpus luteum.

See package insert for complete product information.

Store at controlled room temperature 20°-25° C (68° to 77° F) [see USP].

Warnings: Not for human use. Pregnant women, asthmatics, or persons with bronchial and other respiratory problems should avoid contact with dinoprost tromethamine.

See package insert for additional information.

Note: Spills of LUTALYSE on the skin should immediately be washed off with soap and water.

Each mL contains: dinoprost tromethamine equivalent to 5 mg dinoprost; benzyl alcohol, 9.45 mg added as preservative.

When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid.

NDC 0009-0327-10

One 30 mL Vial

Lutalyse®

Sterile Solution

dinoprost tromethamine injection

Equivalent to

5 mg per mL

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Prostaglandin F_2 alpha for intramuscular use in cattle, #wine and mares.

Restricted Drug-use Only As Directed (California)

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Lutalyse®

Upjohn

brand of dinoprost tromethamine sterile solution

For intramuscular use for estrus synchronization, treatment of unobserved (silent) estrus and pyometra (chronic endometritis) in cattle; for abortion of feedlot and other non-lactating cattle; for parturition Induction In swine; and for controlling the timing of estrus In estrous cycling mares and clinically anestrous mares that have a corpus luteum.

DESCRIPTION

This product contains the naturally occurring prostaglandin F2 alpha (dinoprost) as the tromethamine salt. Each mL contains dinoprost tromethamine equivalent to 5 mg dinoprost: also, benzyl alcohol, 9.45 mg added as preservative. When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid. Dinoprost tromethamine is a white or slightly off-white crystalline powder that is readily soluble In water at room temperature In concentrations to at least 200 mg/mL.

General Biologic Activity: Prostaglandins occur in nearly all mammalian tissues.

Lutalyse dinoprost tromethamine

Lutalyse dinoprost tromethamine sterile solution

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Prostaglandins, especially PGE's and PGF's, have been shown, In certain species, to l) increase at time of parturition, in amniotic fluid, maternal placenta, myometrium, and blood, 2) stimulate myometrial activity, and 3) to induce either abortion or parturition. Prostaglandins, especially PGF2α, have bean shown to 1) increase in the uterus and blood to levels similar to levels achieved by exogenous administration which elicited luteolysis, 2) be capable of creasing from the uterine vein to the ovarian artery (sheep), 3) be related to IUD induced Meal regression (sheep), and 4) be capable of regressing the corpus luteum of most mammalian species studied to date. Prostaglandins have baen reported to result in release of pituitary tropic hormones. Data suggest prostaglandins, especially PGE's and PGF's, may ba involved in the process of ovulation and gamete transport. Also PGF2α has been reported to cause increase in blood pressure, bronchoconstriction, and smooth muscle stimulation in certain species.

SAFETY AND TOXICITY

Laboratory Animals: Dinoprost was non-teratogenic in rats when administered orally at 1.25,3.2, 10.0 and 20.0 mg/kg/day from day 6th-15th of gestation or when administered subcutaneously at 0.5 and 1. 0 mg/kg/day on gestation days 6,7 and 8 or 9, 10 and 11 or 12, 13 and 14. Dinoprost was non-teratogenic In the rabbit when administered either subcutaneously at doses of 0.5 and I. 0 mg/kg/day on gestation days 6,7 and 8 or 9, 10 and 11or 12, 13 and 14 or 15, 16 and 17 or orally at doses of 0.01, 0.1and 1.0 mg/kg/day on days 6-18 or 5.0 mg/kg/day on days 8-1 8 of gestation. A slight and marked embfyo lethal effect was observed in dams given 1.0 and 5.0 mg/kg/day respectively. This wes due to the expected luteolytic properties of the drug.

A 14-day continuous intravenous infusion study in rats at 20 mg PGF2α per kg body weight indicated prostaglandins of the F series could induce bone deposition. However, such bone changes were not observed in monkeys similarly administered LUTALYSE Sterile Solution at 15 mg PGF2α per kg body weight for 14 days.

Cattle: In cattle, evaluation was made of clinical observations, clinical chemistry, hematology, urinalysis, organ weights, and gross Plus microscopic measurements following treatment with various doses up to 250 mg dinoprost administered twice intramuscularly at a 10 day interval or doses of 25 mg administered daily for 10 days. There was no unequivocal effect of dinoprost on the hematology or clinical chemistry parameters measured. Clinically, a slight transitory increase In heart rate waa detected. Rectal temperature was elevated about 1.5° F through the 6th hour after injection with 250 mg dinoprost, but had returned to baseline at 24 hours after Injection No dinoprost associated gross lesions were detected. There was no evidence of toxicological effects. Thus, dinoprost had a safety factor of at least 10X on injection (25 mg luteolytic dose va. 250 mg aafa dose), based on studies conducted with cattle. At luteolytic doses, dinoprost had no effect on progeny. If given to a pregnant cow, it may cause abortion; the dose required for abortion varies considerably with the stage of gestation.

Induction of abortion in feedlot cattle at stages of gestation up to 100 days of gestation did not result In dystocia, retained placenta or death of heifers in the field studies. Tha smallness of the fetus at this early stage of gestation should not lead to complications at abortion. However, Induction of parturition or abortion with any exogenous compound may precipitate dystocia, fetal death, retained placenta and/or metritis, especially at latter stages of gestation.

Swine: In pigs, evaluation was made of clinical observations, food consumption", clinical pathologic determinations, body weight changes, urinalysis, organ weights, and gross and microscopic observations following treatment with single doses of 10, 30, 50 and 100 mg dinoprost administered intramuscularly. The results indicated no treatment related effects from dinoprost treatment that were deleterious to the health of the animals or to their offspring.

Mares: Dinoprost tromethamine was administered to adult mares (weighing 320 to 485 kg; 2 to 20 years old). at the rates of O, 100, 200, 400, and 800 mg per mare per day for 6 days. Route of administration for each dose group was both intramuscularly (2 mares) and subcutaneously (2 mares). Changes were detected in all treated groups for clinical (reduced sensitivity to pain; locomotor incoordination; hypergastromotility; sweating; hyperthermia; labored respiration), blood chemistry (elevated cholesterol, total bilirubin, LDH, and glucose), and hematology (decreased eosinophils; increased hemoglobin. hematocrit, and erythrocytes) measurements. The effects in the 160 mg dose, and to a lesser extent, the 200 mg dose groups were transient in nature, lasting for a few minutes to several hours. Mares did not appear to sustain adverse effects following termination of the side effects.

Mares treated with either 400 mg or 800 mg exhibited more profound symptoms. The excessive hyperstimulation of the gastrointestinal tract caused "a protracted diarrhea. slight electrolyte imbalance [decreased sodium and potassium), dehydration. gastrointestinal irritation, and slight liver malfunction (elevated SGOT, SGPT at 800 mg only). Heart rate was increased but pH of the urine was decreased. Other measurement evaluated in the study remained within normal limits. No mortality occurred in any of the groups. No apparent differences were observed between the intramuscular and subcutaneous routes of administration. Luteoly tic doses of dinoprost tromethamine are on the order of 5 to 10 mg administered on one day, therefore, LUTALYSE was demonstrated to have a wide margin of safely. Thus. the 100 mg dose gave a safety margin of 10 to 20X for a single injection or 80 to 160X for the 8 daily injections.

Additional studies investigated the effects in the mare of single intramuscular doses of O, 0.25, 1.0, 2.S. 3.0, 5.0, and 10.0 mg dinoprost tromethamine. Heart rate, respiration

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Additional studies investigated the effects in the mare of single intramuscular doses of 0, 0.25, 1.0, 2.5, 3.0, 5.0, and 10.0 mg dinoprost tromethamine. Heart rate, respiration rate, rectal temperature, and sweating were measured at 0, 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, and 6.0 hr. after injection. Neither heart rate nor respiration rates were significantly altered ($P > 0.05$) when compared to contemporary control values. Sweating was observed for 0 of 9, 2 of 9, 7 of 9, 9 of 9, and 8 of 9 mares injected with 0.25, 1.0, 2.5, 3,0, 5.0, or 10.0 mg dinoprost tromethamine, respectively. Sweating was temporary In all cases and was mild for doses of 3.0 mg Or less but was extensive (beads of sweat over the entire body and dripping) for the 10 mg dose. Sweating after the 5.0 mg dose was intermediate between that seen for mares treated with 3.0 and 10.0 mg. Sweating began within 15 minutes after injection and ceased by 45 to 60 minutes after injection. Rectal temperature was decreased during the interval 0.5 until 1.0, 3 to 4, or 5 hours after injection for 0.25 and 1.0 mg, 2.5 and 3.0, or 5.0 and 10.0 mg dose groups, respectively. Average rectal temperature during the periods of decreased temperature was on the order of 97.5 to 99.6, with the greatest decreases observed in the 10 mg dose group.

METABOLISM

A number of metabolism studies have been done in laboratory animals. The metabolism of tritium labeled dinoprost (^3H PGF2 alpha) In the rat and in the monkey waa similar. Although quantitative differences wets observed, qualitatively similar metabolizes were preduced. A study demonstrated that equimolar doses of ^3H PGF2 alpha Tham and ^3H PGF2 alpha free acid administered Intravenously to rats demonstrated no significant differences in blood concentration of dinoprost. An interesting observation in tha above study was that the radioactive dose of ^3H PGF2 alpha rapidly distributed in tissues and dissipated in tissues with almost the same curve as it did in the serum. The half-life of dinoprost in bovine blood has been reported to eon the order of minutes. A complete study on the distribution of decline of ^3H PGF2 alpha Tham in the tissue of rats was well correlated with the work done in the cow. Cattle serum collected during 24 hours after doses of O to 250 mg dinoprost have been Assayed by RIA for dinoprost and the 15-keto metabolites. These data support previous reports that dinoprost has a half-life of minutes.

Dinoprost is a natural prostaglandin. All systems associated with dinoprost metabolism exist in the body; therefore, no new metabolic, transport, excretory, binding or other systems need be established by the body to metabolize injected dinoprost.

INDICATIONS AND INSTRUCTIONS FOR USE

Cattle: LUTALYSE Sterile Solution is Indicated as a luteolytic agent.

LUTALYSE is effective only In those cattle having a corpus luteum, i.e., those which ovulated at least five days prior to treatment. Future reproductive performance of animals that are not cycling will be unaffected by injection of LUTALYSE.

1. For Intramuscular Use for **Estrus Synchronization** In Beef Cattle and Non-Lactating Dairy Heifers. LUTALYSE is used to control the timing of estrus and ovulation In estrous cycling cattle that have a *corpus* luteum.

   Inject a dose of 5 mL LUTALYSE (25 mg PGF2α) intramuscularly either once or twice at a 10 to t 2 day interval.

   With the single injection, cattle should be bred at the usual time relative to estrus.

   With the two Injections cattle can be bred after the second injection either at the usual time relative to detected estrus or at about 80 houra after the second injection of LUTALYSE.

   Estrus Is expected to occur 1 to 5 days after injection if a corpus luteum was present. Cattle that do not become pregnant to breeding et estrus on days 1 to 5 after injection will be expected to return to estrus in about 18 to 24 days.
2. For intramuscular Use for Unobserved (Silent) Estrus In Lactating Dairy Cows withaCorpuaLuteum.inject a dose of 5 mL LUTALYSE (25 mg PGF2α) intramuscularly. Breed cows as they are detected in estrus. If estrus has not been observed by 80 hours after injection, breed at 80 hours. If the cow returns to estrus breed at the usual time relative to estrus.

Management Considerations: Many factors contribute to success and failure 01 reproduction.management, and these factors are important also when time of breeding is to be regulated with LUTALYSE Sterile Solution. Some of these factors are:

a. Cattle must be ready to breed- they must have a corpus luteum and be healthy,
b. Nutritional status must be adequate as this has a direct effect on conception and the initiation of estrus In heifers or return of estrous cycles in cows following calving;
c. Physical facilities must be adequate to allow cattle handling without being detrimental to the animal;
d. Estrus must be detected accurately if timed AI is not employed;
e. Semen of high fertility must be used;
f. Semen must be inseminated property.

A successful breeding program can employ LUTALYSE effectively, but a poorly managed breeding program will continue to be poor when LUTALYSE is employed unless other management de ficiencies are remedied first.

Cattle expressing estrus following LUTALYSE are receptive 10 breeding by a bull. Using bulls to breed large numbers of cattle in heat following LUTALYSE will require proper management of bulls and cattle.

3. For Intramuscular Use for Treatment of **Pyometra (chronic endometritis)** in Cattle. Inject a dose of 5mLLUTALYSE (25 mg PGF2α) intramuscularly. In studies conducted with LUTALYSE, pyometra was defined as presence of a corpus luteum in the ovary and uterine horns containing fluid but not a conceptus based on palpation *per rectum*. Return to normal was defined as evacuation of fluid and return of the uterine horn size to 40mm or less based on palpation *per rectum* at 14 and 28 days. Most cattle that recovered in response to LUTALYSE recovered within 14 days after injection. After 14 days, recovery rate of treated cattle was no different than that of non-treated cattle.
4. **For Intramuscular** Use for Abortion of **Feedlot** and **Other** Non. **Lactating Cattle.** LUTALYSE is indicated for its abortifacient effect in feedlot and other non-lactating cattle during the first 100 days of gestation. Inject a dose of 25 mg intramuscularly. Cattle that abort will abort within 35 days of injection.

   Commercial cattle were palpated per *rectum* for pregnancy in six feedlots. The percent of pregnant cattle In each feedlotless than tOO days of gestation ranged between 26 and 84; SO% or more of the pregnant cattle were less than 150 days of gestation. The abortion rates following injection of LUTALYSE increased with increasing doses up to about 25 mg. As examples, the abortion rates, over 7 feedlots on the dose titration study, were 22%. 50%, 71%, 90% and 78% for cattle up to 100 days of gestation when injectedIM with LUTALYSE doses of 0,1(5 mg), 2 (10 mg), 4 (20 mg) and 8 (40 mg) mL, respectively. The statistical predicted relative abortion rate based on the dose titration data, was about 93% for the 5 mL (25 mg) LUTALYSE dose for cattle injected up to lot days of gestation.

Swine: For intramuscular use for parturition induction in swine. LUTALYSE Sterile Solution is indicated for parturition induction In swine when injected within 3 days of normal predicted farrowing.

The response to treatment varies by individual animals with a mean interval from administration of 2 mL LUTALYSE (10 mg dinoprost) to parturition of approximately 30 hours. This can be employed to control the time of farrowing in *sows* and gilts in late gestation.

Management **Considerations:** Several factors must ba considered for the successful use of LUTALYSE Sterile Solution for parturition induction i" swine. The product must be administered at a relatively specific fime (treatment earlier than 3 days prior to normal predicted furrowing may result in increased piglet mortality), It is important that adequate records be maintained on (1) the average length of gestation period for the animals on a specific location. and (2) the breeding and projected farrowing dates for each animal. This Information is essential to determine the appropriate time for administration of LUTALYSE.

Mares: LUTALYSE Sterile Solution is indicated for its luteolytic effect in mares. This luteolytic effect can be utilized to control the timing of estrus in estrous cycling and clinically anestrous mares that have a corpus luteum in the following circumstances:

Lutalyse

Sterile dinoprost tromethamine sterile solution

1. **Controlling Time of Estrus of Estrous Cycling Mares:** Mares treated with LUTALYSE during diestrus (4 or more days after ovulation) will return 10 estrus within 2 to 4 days in most cases and ovulate 8 to 12 days after treatment, This procedure may be utilized as an aid to scheduling the use of stallions.
2. **Difficult-to-Breed Mares:** In extended diestrus there is failure 10 exhibit regular estrous cycles which is different from true anestrus. Many mares described as anestrus during the breeding season have serum progesterone levels consistent with the presence of a functional corpus luteum.

A proportion of "barren", maiden, and lactating mares do not exhibit regular estrous cycles and may be in extended diestrus. Following abortion, early fetal death and

(continued below)

(continued *from above)*

resorption, or as a result of 'pseudopregnancy", there may be serum progesterone levels consistent with a functional corpus luteum.

Treatment of such mares with LUTALYSE usually results In regression of the corpus luteum followed by estrus and/or ovulation. In one study with 122 Standardbred and Thoroughbred mares in clinical anestrus for *an average* of 58 daya and treated during the breeding season, behavioral estrus was detected In 81 percent al an average *time* of 3.7 days after injection with 5 mg LUTALYSE; ovulation occurred an average of 7.o days alter treatment. Of those mares bred, 59% were pregnant following an average of 1.4 services during that estrus.

Treatment of "anestrous" mares which abort subsequent to 38 days of pregnancy may not result in return to estrus due to presence of functional endometrial cups.

WARNINGS

Not for human *use.*

Women of child-bearing age, asthmatics, and persona with bronchial and other respiratory problems should exercise extreme caution when handling this *Product. In* the early stages, women may be unaware of their pregnancies. *Dinoprost* tromethamine is readily absorbed through the skin and can cause abortion and/or bronchiospasms. Direct contact with the skin should, therefore, be avoided. Accidental spillage on the akin should be washed off immediately with soap and water.

Uae of this product in excess of the approved dose may result *In* drug residues.

PRECAUTIONS

Cattle: Do not administer to pregnant cattle unless abortion la desired.

Do not administer Intravenously (I.V.), as this route might potentate adverse reactions.

Cattle administered a *progestogen* would be expected to hava a reduced response to LUTALYSE Sterile Solution.

Aggressive antibiotic therapy should be employed at the first sign of infection at the Injection site whether localized or diffuse. As with all parenteral products careful aseptic techniques should be employed to decrease the possibility of post injection bacterial infections.

Swine: Do not administer to Sows and for gilts prior to 3 daya of normal predicted farrowing, as increased number of stillborn and postnatal mortality may result.

Mares: LUTALYSE Sterile Solution is ineffective when administered prior to day-5 after ovulation.

Pregnancy status should be determined prior to treatment, since LUTALYSE has been *reported to* Induce abortion and parturition when sufficient doses were administered.

Mares should not be treated if they suffer from either acute or subacute disorders of the vascular system, gast rointestinal tract, respiratory system, or reproductive tract.

Do not administer by Intravenous route.

Nonsteroidal anti-InfJammatory drugs (i.e., indomethacin) may inhibit prostaglandin synthesis, therefore these drugs should not be administered concurrency.

ADVERSE REACTIONS

Cattle:

1. The most frequently observed aide effect is Increased rectal temperature at a 5X or 10X overdose. However, rectal temperature change has been transient In all cases observed and hea not been detrimental to the animal.
2. Limited salivation has been reported in some instances.
3. Intravenous administration might Increase heart rate.
4. Localized past injection bacterial infections that may become genera lized have bean reported. In rare instances such infections have terminated fatally. Sea PRECAUTIONS.

Swine: The moat frequently observed aide effects wera erythema and pruritus, slight incoordination, nesting behavior, itching. urination, defamation, abdominal muscle spasms, tall movements, hyperpnea or dyspnea, increased vocalization, salivation, and at the 100 mg (1 OX) dose only, possible vomiting. These side effects are transitory, lasting from 10 minutes to 3 hours, and were not. detrimental to tha health of the animal.

Mares: The most frequently observed aide' effects are sweating and decreased rectal temperature. However, these have bean transient In all cases observed and have not been detrimental to the animal. Other reactions seen have been increase in heart rate, increase in respiration rate, some abdominal discomfort, locomotor incoordination, and lying down. These effects are usually seen within 15 minutes of injection and disappear within one hour. Mares usually continue to eat during the period of expression of side effects. One anaphy lactic reaction of several hundred mares treated with LUTALYSE Sterile Solution wss reported but was not confirmed.

IMPORTANT

Cattle: No milk discard or preslaughter drug withdrawal period is required for labeled uses.

Swine: No preslaughter drug withdrawal period is required for labeled uses.

Mares: Not for use in horses intended for food.

DOSAGE AND ADMINISTRATION

Cattle: LUTALYSE Sterile Solution is supplied at a concentration of 5 mg dinoprost per mL. LUTALYSE is luteolytic in cattle at 25 mg (5 mL) administered intramuscularly. As with any multidose vial, practice aseptic techniques i" withdrawing each dose. Adequately clean and disinfect the vial closure prior to entry with a sterile needle.

Swine: LUTALYSE Sterile Solution will induce parturition in swine at 10 mg

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Swine: LUTALYSE Sterile Solution will induce parturition in swine at 10 mg (2 mL) when injected intramuscularly.

As with any multidose vial, practice aseptic techniques in withdrawing each dose. Adequately dean and disinfect the vial closure prior to entry with a sterile needle.

Mares:

1. Evaluate the reproductive status of the mare.
2. Administer a single intramuscular injection of 1 mg per 100 lbs (45.5 kg) body weight which is usually 1 mL to 2 mL LUTALYSE Sterile Solution.
3. Observe for signs of estrus by means of daily teasing with a stallion, and evaluate follicular changes on tha ovary by palpation of the ovary *per rectum.*
4. Some clinically anestrous mares will not express estrus but will develop a follicle which will ovulate. These mares may become pregnant if inseminated at the appropriate time relative to ovulation of the follicle.
5. Breed mares in estrus in a manner consistent with normal management.

Dinoprost tromethamine is administered once as a single intramuscular injection of 1 mg per 100 lbs (45.5 kg) body weight which is usually 1 mL to 2 mL of LUTALYSE containing 5 mg dinoprost as the tromethamine salt per milliliter.

HOW SUPPLIED

LUTALYSE Sterile Solution is available in 10 and 30 mL vials.

STORAGE CONDITIONS

Store at controlled. room temperature 20° to 25°C (68° to 77" F) [see USP].

Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Pharmacia & Upjohn Company • Kalamazoo, Michigan 49001, USA

Revised August 1996

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